UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,296	11/28/2000	Paul W. Doetsch	25-98A	4866

7590 09/20/2002

GREENLEE, WINNER AND SULLIVAN, P.C.
Suite 201
5370 Manhattan Circle
Boulder, CO 80303

EXAMINER
WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/20/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,296	DOETSCH ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/01/02/*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *16-20* is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09/18/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Amendment under 37 CFR 1.111 filed on July 1, 2002, as paper 11, is acknowledged. The amendments to the specification and claims have been entered as requested. Claims 1-15 are cancelled. Claims 16-20 are amended. Claims 16-20 are pending in the application and are the subject of this Office Action.

Office Action

1. Objections

Objections to claims 16 and 19 made in the previous Office Action, paper No. 9 are withdrawn because the claims have been amended.

The examiner acknowledges formal drawings filed on September 1, 2001. The drawings are approved.

2. Rejections

2.1. Lack of utility, 35 USC section 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 16-20 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The claims are directed to the method for cleavage a double–stranded DNA molecule containing broad scope of DNA lesions wherein the proteins used for cleavage are identified by SEQ ID NOs: 36, 37, 38, 39.

According to information o page 43 of the specification, the sequences have been identified by BLAST searching of sequence databases using UVDE amino acid sequence. Thus, SEQ ID NOs: 36, 37, 38, 39 are homologs of *S. pombe* UVDE.

Although Applicants assure that the sequence analysis indicates that the claimed proteins are UV endonucleases, they do not disclose any functional characteristics of said protein. Even their homology to *S. pombe* UVDE is unknown because the specification is lacking Table 19. Thus, although Applicants assert the polypeptides of SEQ ID NOs: 36, 37, 38, 39 are new UV endonucleases from *N. crassa, B. subtilis*, *Homo sapiens* and *D. radiodurans*, respectively, their biologic role and significance are not disclosed.

Applicants propose to use the polypeptide for cleavage of damaged DNA, however, the specific enzymatic activity of said polypeptides is not supported in the specification because **Applicants do not teach results of any enzymatic assay that was used to prove the activity of these novel endonucleases.**

After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. Thus, there has been no immediately apparent or "real world" utility identified as of the filling date of the instant application. Until an actual and specific biologic significance can be attributed to the protein and its gene, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention.

Claims 16-20 are also rejected under 35 USC § 112, the first paragraph. Since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention, so that it would operate as intended, without undue experimentation.

2.2. 35 USC section 112, second paragraph

Rejection of claims 17 and 19 made under this paragraph in the previous Office Action, paper No. 9 is withdrawn because the claims have been amended.

The examiner suggests to change the language in the 9 line of the amended claim 16 to the one used in claim 18, i. e., "SEQ ID NO: 2, amino acids 230-828, wherein said endonuclease is purified".

2.3. 35 USC section 102

Claims 16, 18, and 20 remain rejected under 35 U.S.C. 102(b) as being anticipated by Takao et al. (Nucleic Acid Res. **1996**, 24, 1267-1271).

The claims are directed to the method for cleavage a double–stranded DNA molecule containing a distorted structure when the cleavage enzyme consists of amino acids 230-828 of SEQ ID NO: 2.

In their response, page 8, Applicants write: "this reference teaches that the truncated endonuclease was not stable in pure form, and the assays were carried out with endonuclease preparations which were only about 35% pure. By contrast, the

present application teaches that the truncated UVDE proteins were purified to apparent electrophoretic homogeneity and that proteins made were stable in pure form".

Applicants' arguments have been fully considered, but they are found not persuasive. Takao et al. cloned the gene of *S. pombe* UVDE endonuclease having the sequence identical to SEQ ID NO: 2. Takao et al. also showed that truncation of the protein up to 232 amino acid from the N-terminus does not influence the endolytic activity of the enzyme on UV irradiated DNA. Takao et al. expressed the protein consisting of amino acid 230-828 of SEQ ID NO: 2 in *E. coli* and further used the truncated protein for incision of the UV irradiated DNA. Takao et al. experienced difficulties with purification of the yeast protein expressed in *E. coli*, whereas Applicants, who used as a host *S. cerevisiae* and expression of the truncated UVDE gene in frame with a glutathione-S-transferase leader sequence, a method assuring the expression of a stable protein, were successful in purification of the expressed protein to apparent electrophoretic homogeneity. Although Takao at al. used in the same method the enzyme that was not 100% pure, the fact is that the enzyme (product) and the method of use of said product were taught by Takao et al. two years before Applicants filled, on June 8, 1998, the provisional application No. 60/088521, of which the instant application claims benefit.

Claims 16, 18 and 20 remain rejected under 35 U.S.C. 102(b) as being anticipated by Yajima et al (The EMBO Journal **1995**, 14, 2393-2399.

The claims are directed to the method for cleavage a double–stranded DNA molecule containing a distorted structure when the cleavage enzyme has the amino acid sequence of SEQ ID NO: 36.

In their response, page 9, Applicants write: "The first incision assay taught at page 2399 is one in which closed circular plasmid DNA has been UV-irradiated. The second assay is in which oligonucleotides with pyrimidine dimers have been UV-irradiated [emphasis MW]." Further Applicants add, "Applicants have amended claims 16 and 18 to specify that when the endonuciease has the amino acid sequence given in SEQ ID NO: 36, and that the distortion is due not to a photoproduct in an oligonucleotide or in a closed circular plasmid DNA."

Applicants' arguments have been fully considered but are found not persuasive. Yajima et al. cloned the gene encoding the UV specific endonuclease of *Neurospora crassa* having the amino acid sequence identical to SEQ IDS NO: 36 of the instant application. In the first assay taught on page 2399 Yajima et al. use, indeed, a closed circular plasmid. In the second assay, on the same page, they use an oligonucleotide that was synthesized to be specifically used for substrate and site determination of the enzyme. However, in both assays the damage was induced by irradiation with UV. Close reading of the text of the article reveals that Yajima et al., also treated with the enzyme the plasmid that was linearized before irradiation, page 2395, right column, line 20. Therefore, Yajima et al used three forms of UV irradiated DNA. Limiting usage of the claimed method to a particular form of DNA is impractical. One skilled in the art,

having an endonuclease specific for damaged DNA does not limit its uses to a particular form of the damaged DNA.

In conclusion, Yajima et al. teach the product, i.e. the enzyme of SEQ ID NO: 36 and its use in the method for cleavage of damaged double stranded DNA three years before Applicants filed, on June 8, 1998, the provisional application No. 60/088521, of which the instant application claims benefit. The rejection under 35 USC section 102 is, therefore, not withdrawn.

As to SEQ ID NO: 38 towards claims 16, 18 and 20 are directed, Applicants' arguments presented on page 9 are fund persuasive and rejection under 35 USC section 102 is changed to rejection under section 103; see below.

New Rejection

Claims 16-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Takao et al. (Nucleic Acid Res. **1996**, 24, 1267-1271). The claims are directed to the method for cleavage a double–stranded DNA molecule containing a distorted structure when the cleavage enzyme has the amino acid sequence of SEQ ID NO: 4.

Takao et al. cloned *S. pombe* UVDE endonuclease gene having the sequence identical to SEQ ID NO: 2 of the instant application, said sequence consists of 599 amino acids. Takao et al. showed that the protein truncated up to 229 amino acid from the N-terminus (page 1270 Figure 5 B) retains enzymatic activity towards UV irradiated DNA. SEQ ID NO: 4 of the instant application, called by Applicants "delta 228 variant" is identical to the truncated form of the enzyme consisting of amino acids 229-599 as

shown in Figure 5 B of the prior art. Takao et al also teach on page 1268 the incision assay for their UVDE endonuclease. Thus, claims 16-20 are rejected under 35 USC, section 102(b) because SEQ ID NO:4 and the claimed method of its use are anticipated by Takao et al.

2.4. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 16, 18, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellacosa et al, Proc. Natl. Acad. Sci. USA, 1999, 96, 3969-3974 (published March 1999) and further in view of common knowledge in the field of DNA repair and practice in DNA repair studies.

The claims are directed to the method for cleavage a double–stranded DNA molecule containing a distorted structure when the cleavage enzyme has the amino acid sequence of SEQ ID NO: 38.

Bellacosa et al. disclose the endonuclease having the amino acid sequence identical to SEQ ID NO: 38 of the instant application; Figure 2, page 3972. The endonuclease called MED1 is a novel human methyl-CpG-binding endonuclease that

interacts with DNA mismatched repair protein MLH1. In their article Bellacosa and co-workers do teach the incision assay of the DNA at page 3970. Bellacosa et al do not teach results of use of the enzyme and assay in case of UV damaged DNA. However, the authors suggest clarifying the role of the new enzyme in the miss matched repair pathway and predict, on the bases of homology to bacterial damage-specific glycosylases/lyases, the possibility that MED1 functions in a pathway of base excision repair; page 3974, right column, line 13.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the endonuclease disclosed by Bellacosa et al. and apply it in the assay for cleavage of DNA irradiated with UV, or other DNA damaging agent, because DNA repair processes involve miss matching of nucleotides pairing.

The motivation, suggested by Bellacosa, would be the use of the enzyme in characterization of the mismatch repair process in human as well as a possible medicinal use.

The expectation of success is high because of Bellacosa et al.'s teachings of the enzyme properties.

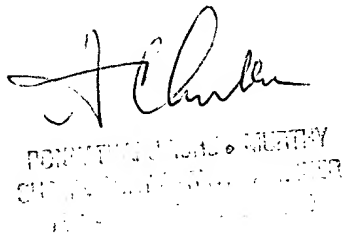
Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was as a whole *prima facie* obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number

is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.



Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Assistant Patent Examiner